CME review

Therapeutic alternatives for chronic urticaria: an evidence-based review, part 1

Matt Morgan, MD,*† and David A. Khan, MD*

Objective: To evaluate the use of alternative therapies for chronic urticaria refractory to first-line treatments in an evidence-based manner.

Data Sources: MEDLINE searches were performed cross-referencing *urticaria* with the names of multiple therapies. Articles were then reviewed for additional citations. Articles published after 1950 were considered.

Study Selection: All articles, including case reports, were reviewed for soundness and relevance.

Results: Experience has been reported for a wide variety of alternative therapies in the treatment of chronic idiopathic and physical urticarias. Evidence for most agents is limited to anecdotal reports. The second-line therapies reviewed are also categorized based on criteria of safety, efficacy, convenience, and cost, in relation to the first-line antihistamines.

Conclusions: Alternative agents should be considered in patients with chronic urticaria who are both severely affected and unresponsive to antihistamines. Although monitoring for toxicity is important in management with many alternative agents, safety is favorable compared with corticosteroids.

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INTRODUCTION

Despite many advances, management of chronic urticaria (CU) remains a formidable challenge for both clinicians and patients. Therefore, we evaluate herein the use of alternative therapies for CU refractory to first-line treatments in an evidence-based manner. MEDLINE searches were performed cross-referencing *urticaria* with the names of multiple therapies. Articles were then reviewed for additional citations. Articles published after 1950 were considered. All articles, including case reports, were reviewed for soundness and relevance. This review covers a comprehensive spectrum of therapies that potentially expand the capability of clinicians to meet the challenge of caring for patients with urticaria. Urticaria lasting longer than 6 weeks and with an autoimmune or idiopathic basis (CIU) is the focus of this review, although relevant experience involving physical urticarias, CU combined with a significant angioedema component, and urticarial vasculitis (UV) is also considered.

Primary recommendations for the management of CU include general measures such as avoidance of any aggravating stimuli, topical antipruritic emollients, reassurance and education, and specific pharmacotherapy, of which the newer selective H_1-antihistamines are the preferred intervention.[1] However, the prior generation "sedating" antihistamines remain useful, efficacious first-line agents for many patients. Some of these nonselective antihistamines have other useful receptor properties that may extend additional efficacy in certain cases. Such agents include doxepin,[2] cyproheptadine,[3] and ketotifen.[4] The H_2-antihistamines are also used in clinical practice, most often as add-on therapy, but these agents generally offer modest incremental efficacy.[5] In addition to combining multiple antihistamines in such a way, higher doses of antihistamines are widely recommended or prescribed[6]; however, the evidence supporting this practice is minimal.[7,8]

First-line therapy with an antihistamine-based regimen is usually efficacious but may not achieve satisfactory control in 5% to as many as 50% of CU patients.[6,9] Corticosteroids

Affiliations: * Division of Allergy & Immunology, University of Texas Southwestern, Dallas, Texas; † Allergy, Asthma, and Immunology of North Texas, McKinney, Texas.

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cannot be considered first-line therapy but are the most widely accepted alternative agent in the treatment of refractory CU despite their adverse effects and absence of specific evidence. Because of toxicity, corticosteroids are strictly reserved for antihistamine failures or the most severe cases. Although highly and reliably efficacious, corticosteroids generally do not have the potential for drug-free remission or to alter the disease course. As such, other alternative agents are required to fill the enormous gap between the benign but occasionally inadequate antihistamines and high-efficacy, high-toxicity corticosteroids.

This review focuses on alternative therapies in the management of refractory CU. The Practice Parameters for the Diagnosis and Management of Urticaria briefly mention a few "alternative management and therapeutic regimens," and this review discusses in depth the evidence for these alternative therapies.[10] As in the Practice Parameters, we also prefer the term *alternative* to encompass a wide variety of therapies that may also be appropriately termed *immunosuppressive*, *immunomodulatory*, or *steroid-sparing*, since not all agents fit these descriptions in all circumstances. Evidence will be drawn from a diverse body of published articles, supplemented sparingly by our own experience. Most alternative therapies for CU continue to rely on anecdotal evidence, open trials, and consensus opinion rather than randomized controlled trials.

In general, we recommend considering alternative agents in the subset of CU patients with severe disease who are intolerant to or in whom high-dose or combination antihistamines have failed. Frequent follow-up by the clinician is important because of the need for close monitoring for toxic effects in patients taking alternative agents for off-label use. Emphasis is placed on practical parameters, including dosage and titration, time to response, possibility of inducing remission, and monitoring required while taking each agent (Table 1). The level of evidence[11] and possible mechanisms of action are also considered. In this article, more preferred therapies are classified as second-line agents based on satisfying a combination of criteria, including safety, efficacy, convenience (including relative freedom from monitoring), and low cost. Additional agents that are otherwise less favored using these criteria or that have insufficient experience will be discussed in part 2 of this review.

ALTERNATIVE THERAPIES FOR REFRACTORY CU: SECOND-LINE AGENTS

Leukotriene Modifiers

The efficacy and, primarily, safety of the leukotriene modifiers have placed these agents at the top of the list of alternative agents, and future practice may place them alongside antihistamines as first-line therapy.[12] Available agents that have been studied include the receptor antagonists montelukast and zafirlukast and the 5-lipoxygenase inhibitor zileuton. Leukotrienes appear to play an important contributory role in urticaria. Injected leukotriene D4 is more potent than histamine in causing a wheal and flare,[13] and leukotriene-mediated urtication is not blocked by other agents.[14] Serum from patients with autoimmune CIU is capable of releasing leukotrienes, in addition to other mediators.[15]

The earliest case reports suggest satisfactory clinical response in many patients with CIU who had been refractory to antihistamines[16] and even corticosteroids[17,18] and other alternative agents.[19] No head-to-head studies have compared different leukotriene modifiers for urticaria, but a single case report described a slight advantage of zileuton over zafirlukast in a patient with aspirin-exacerbated CIU.[20] Most studies suggest fairly rapid response, but an open trial noted time to benefit could be up to several weeks; this was slower than antihistamines in parallel open trials, but formal statistical comparison was not performed.[21] Currently, 5 positive randomized controlled trials support efficacy of zafirlukast[22] and montelukast either singly[23,24] or in combination with antihistamines.[25,26] Several negative studies have also appeared. One randomized controlled crossover revealed no statistical difference between zafirlukast and placebo in 52 CIU patients.[27] Another randomized controlled trial found montelukast less effective than desloratadine for 160 patients with less severe CIU.[28] One study failed to reach completion and is therefore considered a case series describing failure of a 1-week course of montelukast in 8 of 10 CIU patients.[29] The only published experience with pranlukast described 2 patients who experienced an exacerbation during therapy.[30]

Unlike other agents, factors predicting clinical response have been suggested for leukotriene modifiers. Much initial interest appropriately began with CIU associated with aspirin or nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity.[20,31] Case reports described success using montelukast to block acute urticaria secondary to NSAIDs.[32,33] Montelukast was also demonstrated to be more effective than cetirizine and placebo in a randomized controlled trial of 51 patients with NSAID-exacerbated CIU.[24] Another randomized trial found montelukast more effective than placebo, with particular benefit noted for NSAID-exacerbated CIU.[25] Results from 2 randomized controlled trials of 27 and 95 CIU patients have reported that positive autologous serum skin test (ASST) results may predict better response to leukotriene modifiers,[22,23] whereas another open trial found younger age and shorter duration of CIU were more predictive than history of NSAID exacerbation or positive ASST results.[34] Montelukast also exhibited benefit in 3 of 4 patients with unusual cases of antihistamine-induced urticaria.[35]

Experience in physical urticarias has also been promising. Benefit for cold urticaria was described for montelukast in 1 patient.[36] Zafirlukast plus cetirizine was found to be more effective than either agent alone after cold challenges in 2 other patients.[37] After the initial success of montelukast in delayed pressure urticaria (DPU),[38] 2 randomized controlled trials demonstrated superiority of montelukast plus loratadine vs loratadine alone[39] and montelukast plus desloratadine vs desloratadine alone or placebo[40] for DPU.

Table 1. Second-Line Alternative Agents for the Treatment of Chronic Urticaria

Class of agent and described doses and regimens	Time to response	Time to relapse	Potential for remission	Adverse effects	Suggested monitoring	Level of evidence/ strength of recommendation[11]
Leukotriene modifier						
Montelukast, 10 mg orally every 24 h Zafirlukast, 20 mg orally every 12 h Zileuton, 600 mg orally every 6 h	Several days to 1 week	Several days	±	Headache, gastrointestinal complaints	Baseline: for zileuton, liver enzymes; follow-up: same, monthly for first 3 months, then every 3 months for remainder of first year, then periodically	Ib/A
Sulfone						
Dapsone, 25–150 mg/d orally	Several days to several weeks	Several days	++	Dose-related anemia, peripheral neuropathy, rash, gastrointestinal complaints; rarely, methemoglobinemia and blood dyscrasias, dapsone hypersensitivity syndrome; avoid: patients with hemoglobin M or low levels of G6PD or methemoglobin reductase	Baseline: G6PD level, renal function ± urine analysis, liver enzymes, blood cells counts; follow-up: blood cell counts 1–2 weeks after starting, then periodically	IIb/B
5-Aminosalicylic acid						
Sulfasalazine, 500 mg/d orally then titrate up to effective dose of 2 g/d orally divided Olsalazine, up to 1.5 g/d orally divided	Several days to several weeks	Several days	+	Headache, gastrointestinal complaints, reversible oligospermia; rarely, rash, photosensitivity, proteinuria, cytopenias, cyanosis, hepatotoxicity (adverse effects more common above 3–4 g/d)	Baseline: G6PD, blood cell counts, liver enzymes, renal function with or without urine analysis; follow-up: blood cell counts monthly for first 3 months then periodically	III/C
Chloroquine						
Hydroxychloroquine, 200 mg orally every 12 h	1 to 3 months	Unknown	±?	Gastrointestinal complaints; rarely, retinal and nonretinal ocular reactions, myopathy; caution: children and patients with porphyria, psoriasis, low levels of G6PD; retinitis may initially be asymptomatic	Baseline: blood cell counts, renal function, liver enzymes; baseline eye examination for planned treatment with higher doses or long duration; follow-up: periodic eye examinations if higher dose or long duration; attention to any ocular complaints	Ib/C
Colchicine						
Colchicine, 0.6 mg orally every 12 h	Several days to 1 month	Several days	±?	Gastrointestinal complaints, stomatitis, marrow depression, rash, peripheral neuropathy, alopecia	Baseline: blood cell counts, renal function, liver enzymes; follow-up: blood cell counts periodically	III/D

Table 1. Continued

Class of agent and described doses and regimens	Time to response	Time to relapse	Potential for remission	Adverse effects	Suggested monitoring	Level of evidence/ strength of recommendation[11]
Calcineurin inhibitor						
Cyclosporine, 2.5–5 mg/kg orally daily divided; titrate to lowest effective dose	2 days to several weeks	1 day to several weeks	++	Gastrointestinal complaints, headache, tremor, renal dysfunction, hypertension, hyperlipoproteinemia, hirsutism, gingival hyperplasia, leukopenia, neuropathy; rarely dose-dependent immune suppression-related infections and neoplasia	Baseline: blood pressure, renal function, electrolytes, lipoproteins, liver enzymes; follow-up: blood pressure, renal function, electrolytes at least monthly for first 3 months then periodically; consider drug levels about every 3 weeks in some patients (cyclosporine <300 ng/mL; tacrolimus <20 μg/mL)	Ib/A
Tacrolimus, 0.025–0.2 mg/kg daily orally divided; titrate to lowest effective dose						
Mycophenolate						
Mycophenolate, 1–2 g/d orally divided	Several weeks?	Unknown	++?	Gastrointestinal complaints; rarely leukopenia, anemia, dose-dependent immune suppression-related infections	Baseline: blood cell counts, liver enzymes; follow-up: blood cell counts periodically	IIb/C
Corticosteroid[a]						
Prednisone, up to 1 mg/kg daily (not to exceed 80 mg/d) or equivalent dose of other agent; titrate quickly to lowest effective dose	Several days to 1 week	Variable	–	Mood alteration, adipose and fluid weight gain, hypertension, hyperglycemia, hyperlipoproteinemia, cataracts, raised intraocular pressure, headache, gastrointestinal complaints, dermal atrophy, osteopenia, infections; caution: children, preexisting psychiatric disorders, diabetes	Baseline: consider glucose, mental status examination, blood pressure, lipoproteins; follow-up: same, periodically	IV/D

Symbols: −, none; ±, unlikely; +, slight possibility; ++, may be expected in some patients; ?, uncertainty due to sparse evidence.
[a] Listed for comparison purposes.

Leukotriene modifiers are currently the best-studied group of alternative agents. Excellent safety, absence of required monitoring in the case of montelukast and zafirlukast, and wide availability make leukotriene modifiers the preferred alternative agent to try. Although one study suggested persistent drug-free remission,[25] most experience argues against such a disease-modifying effect. Leukotriene modifiers appear to be useful as both monotherapy and add-on therapy but are not likely to displace antihistamines from their role as first-line therapy. In our experience, leukotriene modifiers may provide improvement in some cases of antihistamine-resistant CU that may be sufficient to bring about adequate control.

Dapsone

Until recently, experience with dapsone was based on numerous case reports of success in UV.[41–43] In 1 case, addition of pentoxifylline, 1,200 mg/d, converted a partial response on dapsone, 100 mg/d, to a complete response over several weeks.[44] In another report, a patient with UV in whom hydroxychloroquine therapy had failed responded to dapsone, 100 mg/d, within 1 week but then developed apparent wors-

ening of UV, which was identified as the dapsone hypersensitivity syndrome.[45] Certain cases of UV and CIU may have neutrophil-rich histology on biopsy, which would support the traditional view that dapsone is advantageous in cutaneous diseases in which neutrophils are thought to play a role.[46] A recent series of UV patients described incomplete response in 1 patient with neutrophilic urticaria taking dapsone and colchicine.[47] Dapsone possesses a variety of possible effects whose spectrum may encompass both vasculitic and nonvasculitic urticaria. These effects include suppression of prostaglandin and leukotriene activity, interference with release or function of lysosomal enzymes[48] and myeloperoxidase generation of toxic halides,[49] disruption of integrin-mediated neutrophil adhesiveness,[50] inhibition of signals to recruit and activate neutrophils,[51] and scavenging of oxygen free radical intermediates.[52]

Experience also exists for dapsone in the treatment of nonvasculitic CU. A series of 5 patients with DPU had excellent response to lower doses (50 mg/d but as low as 50 mg every other day).[53] In a few, dapsone appeared to have a true immunomodulatory effect with persistent drug-free remissions. A single patient with CIU was also described as enjoying remission that lasted at least 1 year after stopping use of the drug.[54] Another patient with isolated angioedema refractory even to prednisone responded to dapsone, 50 mg/d, within 1 month and had a durable remission for at least 1 year.[55] A larger case series of 11 CIU patients demonstrated excellent clinical response within several weeks in 9 (ultimately allowing discontinuation of cetirizine therapy) with a low dose of 25 mg/d.[56] In the other 2 patients, the dose was increased to 50 mg/d, which converted one to complete response and the other to partial. The authors noted 7 of these 11 had lasting remission at variable follow-up times. Preliminary results from our own randomized, double-blind, placebo-controlled, crossover study indicate improvement in 15 of 22 CIU patients taking dapsone, 100 mg/d (M.M., unpublished data, 2007). Response appeared to be fairly rapid, but some patients required several weeks to notice improvement.

Despite required monitoring for the predictable small decline in hemoglobin, dapsone is generally well tolerated and has a favorable adverse effect profile. Before initiating dapsone, we recommend obtaining a glucose-6-phosphate dehydrogenase (G6PD) level to avoid more severe hemolytic anemia in G6PD-deficient patients. Most intriguing is the possibility of sustained remission after stopping use of the drug, which we have also observed in responders. Wide availability and low cost are additional advantages that make dapsone an excellent second-line agent. Whether the widely held belief that neutrophilia apparent on skin biopsy specimens is predictive of better response to dapsone remains unproven.

Sulfasalazine

Sulfasalazine has been used in the treatment of CU despite relatively sparse but promising published experience. Mechanisms of action with possible relevance in CU include anti-inflammatory effects mediated by adenosine release,[57] decreased leukotriene and prostaglandin synthesis, inhibition of IgE-mediated mast cell degranulation by the 5-aminosalicylate metabolite,[58] attenuation of the respiratory burst,[59] and inhibition of early-phase events in the proliferation and differentiation of B-lymphocytes.[60] Two early reports covering a total of 4 CIU patients (in 1 of whom phototherapy and montelukast had failed) described an impressive 100% response rate, with a minimum therapeutic dose of 2 to 3 g/d. Patients remained symptom free while taking sulfasalazine but relapsed rapidly after stopping use of the drug or reducing the dose.[61,62] Sulfasalazine has also been reported to be beneficial in 2 patients with DPU, who successfully remained symptom free while taking 2 g/d.[63]

The largest observational series described retrospectively 14 of 19 CIU patients who experienced significant improvement, with 4 others showing more modest benefit and 1 worsening.[64] Several patients were able to stop taking other medications or even exhibit remission of CU with cessation of sulfasalazine. Response occurred within 1 month, in the context of a typical gradually escalating dose protocol. Dosages above 2 g/d had no additional clinical benefit. A single patient mentioned separately had significant improvement while taking olsalazine, 1.5 g/d. Case reports describing success with other agents have mentioned failure to sulfasalazine in passing.[38] Drawbacks to sulfasalazine therapy include laboratory monitoring and the advisability of titrating to the full therapeutic dose, which may prolong the latency time between starting therapy and clinical response. Coadministration of folate may be considered. Overall, sulfasalazine is well tolerated by most patients and appears to be effective in some cases, but further study is warranted.

Hydroxychloroquine

Originally developed as antimalarials, hydroxychloroquine and chloroquine are now more widely used for anti-inflammatory applications. Multiple potential antiurticarial mechanisms include suppression of T-lymphocyte activation[65] and disruption of antigen processing and other cellular processes by alkalinization of intracellular vacuoles.[66] Chloroquine was first reported to be modestly effective in the treatment of solar urticaria nearly 4 decades ago,[67] but failure has also been described.[68] Other published cases describe variable experience with hydroxychloroquine in UV, including 1 successful response in a patient in whom azathioprine therapy had failed[69] and other patients who did not respond to hydroxychloroquine.[45,70,71]

A single randomized controlled trial of patients with CIU demonstrated improvement in quality of life in the hydroxychloroquine arm.[72] The authors observed a trend toward reduced medication use and urticarial activity and noted the study was not sufficiently powered (18 patients completed the study) to render significance. An appropriately longer duration of 3 months was used in this study, because a potential disadvantage of hydroxychloroquine seen also in other applications is that patients may require weeks to months to reach

peak effect. Recent opinion suggests routine ophthalmologic monitoring is not required for patients taking hydroxychloroquine at lower doses; there is less consensus about baseline examinations, but the relatively brief duration of use expected for therapeutic trials in CIU weighs against this for most patients.[73] Overall, comparative safety and low cost make hydroxychloroquine a reasonable second-line choice. One strategy we have used to overcome the long latency time is to start hydroxychloroquine therapy with a different agent with nonoverlapping toxicity; evaluation of response to each agent may be determined based on the expected differential response times.

Colchicine

Colchicine is not infrequently used by urticaria specialists; nonetheless, the published record on colchicine for CU has been disappointing. Possible relevant mechanisms of action include suppression of leukotriene generation[74] and decrease in leukocyte adhesiveness and migration.[75] The single available randomized controlled trial failed to demonstrate therapeutic difference between colchicine and placebo (with crossover) in 12 evaluable patients with primarily DPU. However, the authors noted this trial was underpowered to detect only a "major effect" using their methods. Subjectively more patients reported improvement with colchicine (n = 5) than placebo (n = 1), but 6 found no difference.[76] The other report in the literature found colchicine ineffective for familial cold urticaria.[77] Other reports suggest colchicine can be effective in UV,[47,70] including where other alternative agents have failed or produced an inadequate response.[71,78] Failure for UV has been reported elsewhere.[43]

Despite the sparse available evidence in CIU, we have observed clinical responses attributable to colchicine in CIU patients, albeit infrequently. Colchicine has a number of relative advantages, including a favorable safety profile at recommended doses, minimal requirements for monitoring, low cost, and generally rapid onset of action. Further investigation is required to confirm its exact role in refractory CIU.

Calcineurin Inhibitors

Calcineurin inhibitors, particularly cyclosporine**,** have been used successfully in urticaria. A wide spectrum of possible antiurticarial mechanisms has been described, including inhibition of calcium-dependent release of and responsiveness to histamine, leukotriene C4, and other mediators in various cell types, including mast cells.[79] Many of these hypothesized effects target the mast cell, but anti–T-lymphocyte activity with resultant disruption of autoantibodies and interaction with mast cells may be another mechanism of action in urticaria.[80] Cyclosporine may also disrupt tumor necrosis factor α activity and secondarily inhibit neutrophil accumulation.[81] Tacrolimus likely shares many therapeutic effects.

The first published experience described significant improvement in 3 patients (2 also with an angioedema component), but these patients discontinued therapy because of intolerance of the relatively high dose used (6 mg/kg daily), with relapse of their CIU.[82] Nearly all subsequent studies have used more moderate doses, including a strategy of starting high and tapering down to a lower tolerated dose,[68,83–87] and it appears that such careful titration of the daily dose is key to achieving an optimal benefit-to-risk ratio. Published experience of cyclosporine in physical urticarias has been limited. Chronic cold urticaria remitted with 3 mg/kg daily in 1 patient, who was then able to be maintained with a dose of 1.7 mg/kg daily, a much lower dose than that documented in CIU.[88] Cyclosporine has also been successful in raising the minimum urticating dose in a patient with solar urticaria.[68]

Randomized controlled trials have supported the efficacy of cyclosporine, but some uncertainty persists regarding duration of therapy. Some authors advocate longer therapy to sustain benefit,[83,87,89] with published follow-up in the literature extending out as far as a mean of 11 years,[90] whereas others suggest most of the benefit is apparent by the initial month of treatment.[91] As with other alternative agents, currently no promising means of predicting response in advance is available. At this time, we would not recommend a routine ASST as a predictive tool, because the available large studies have found no correlation with response to cyclosporine.[91,92] Most published reports suggest a number of notable advantageous properties of cyclosporine. These properties include rapid onset (sometimes within days),[83,85,88] possibility of long-lasting remission,[86,88,93] and degree of efficacy comparable to prednisone,[94] including versatility to be used for short-term control of flares.[85] Adverse effects are frequent and often dose related but generally not severe and sometimes amenable to dose reduction rather than necessitating cessation of therapy.

Newer calcineurin inhibitors and related agents are widely used for similar indications as cyclosporine, but experience in CIU remains limited. Stanaland[95] related "good to excellent" results with open use of tacrolimus in a small group of CIU patients at doses of 0.05 to 0.2 mg/kg daily; however, these observations were mentioned in passing and not described in detail. Adverse effects were noted to be fewer when compared with treatment with cyclosporine. Tacrolimus has been shown to have a slight edge over cyclosporine in terms of cardiovascular and "cosmetic" adverse effects in transplantation[96] but possibly more neurologic and gastrointestinal problems.[97] Whether this applies to the lower doses and shorter durations of treatment in CIU remains to be seen. Recently, the first published documentation of tacrolimus for CIU became available.[98] In this open series, a response rate of 70% was observed, which is likely comparable to cyclosporine. The authors noted a single responder who had lasting drug-free remission had earlier failed to respond to cyclosporine. Clearly, the question of whether cyclosporine and tacrolimus, as well as other related agents such as sirolimus and ascomycin, exhibit cross-efficacy requires further study.

Overall, calcineurin inhibitors hold great promise as efficacious alternative agents for refractory CIU. A growing body of published reports is available, including randomized

controlled trials, almost all involving CIU. Although specific evidence has not yet extended to other varieties of CU, calcineurin inhibitors likely have a broad spectrum of activity. Monitoring of more parameters is required for these expensive drugs than for other agents, and experience with diagnosing and managing possibly serious adverse effects is important. However, the potential benefits of rapid control, high degree of efficacy in responders, and occasional long-term remission cannot be overlooked. In light of these factors, we typically reserve calcineurin inhibitors for patients in whom 1 or more of the aforementioned other second-line agents have failed.

Mycophenolate

Mycophenolate is a newer agent that has rapidly found wide application in transplantation and selected use in various cutaneous disorders. Mycophenolate acts as an antimetabolite selectively for lymphocytes and also impairs expression of adhesion molecules and secondary leukocyte migration.[99] The first published case described mycophenolate as maintenance therapy for 2 patients with UV after initially achieving remission with cyclophosphamide.[100] At a dose of 2 g/d for at least 15 months, there were no described adverse effects or relapse. Use of mycophenolate at a dose of 1 g twice daily has recently been described in 9 CIU patients.[101] Treatment in this open series was continued for 12 weeks. According to urticaria scores, 6 of 9 experienced marked improvement, but the authors noted all patients had benefit that was steroid-sparing and persisted for at least 6 months after discontinuation. No adverse effects or laboratory abnormalities were reported. Although unrelated to the calcineurin inhibitors, mycophenolate shares certain of the same properties with the promise of fewer adverse effects. If confirmed, this would make mycophenolate a highly attractive alternative to the calcineurin inhibitors, but further experience is needed.

CONCLUSION

Antihistamines in varying doses and combinations are often effective in controlling CU. However, for the common problem of CU refractory to antihistamines, successful application of alternative therapies is appropriate and preferable to long-term use of systemic corticosteroids. The major second-line agents reviewed herein in the context of CU not responsive to antihistamines represent expanded treatment options that benefit both clinicians and patients who must manage this frustrating disorder.

The choice of such alternative agents and sophistication in their application have steadily expanded, although the level of evidence has not kept pace. Questions that have not been adequately addressed include predictive factors that allow individualized selection of alternative therapies, the optimal sequence of therapies to consider in the current trial and error paradigm, and whether agents with nonoverlapping mechanisms of action and toxicities may fail when used singly but bring about symptom control when used in combination. It is ultimately left to the clinician to synthesize the available data on the wide selection of agents covered herein and in part 2 and to monitor for and manage potential toxic effects. Understanding the potential role for these alternative agents in treating CU is important even for practitioners who do not use such agents in routine practice.

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Requests for reprints should be addressed to:
David A Khan, MD
Division of Allergy & Immunology
University of Texas Southwestern
5323 Harry Hines Blvd
Dallas, TX 75390-8859
E-mail: dave.khan@utsouthwestern.edu

Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor medical education for physicians. ACAAI designates each Annals CME Review Article for a maximum of 2 *AMA PRA Category 1 Credits*™. Physicians should only claim credits commensurate with the extent of their participation in the activity.

CME Examination

1–5, Morgan M, Khan DA. 2008;100:403–412.

CME Test Questions

1. Which of the following is the most common laboratory abnormality in patients undergoing dapsone therapy?
   a. anemia
   b. hypokalemia
   c. hyponatremia
   d. methemoglobinemia
2. Which of the following medications has the highest level of evidence for efficacy in chronic urticaria?
   a. colchicine
   b. cyclosporine
   c. mycophenolate
   d. sulfasalazine
3. The level of evidence for efficacy of systemic steroids in chronic urticaria is based on:
   a. meta-analysis
   b. randomized controlled studies
   c. case-control studies
   d. anecdotal experience
4. A patient with antihistamine-resistant chronic urticaria and G6PD deficiency would best tolerate which of the following medications?
   a. dapsone
   b. hydroxychloroquine
   c. mycophenolate
   d. sulfasalazine
5. Which of the following medications would have the most rapid onset of action and the greatest potential for remission of chronic urticaria?
   a. cetirizine
   b. cyclosporine
   c. hydroxychloroquine
   d. montelukast

Answers on page 468.

Therapeutic alternatives for chronic urticaria: an evidence-based review, part 2

Matt Morgan, MD,*† and David A. Khan, MD*

Objective: To evaluate the use of alternative therapies for chronic urticaria refractory to first-line treatments in an evidence-based manner.

Data Sources: MEDLINE searches were performed cross-referencing *urticaria* with the names of multiple therapies. Articles were then reviewed for additional citations. Articles published after 1950 were considered.

Study Selection: All articles, including case reports, were reviewed for soundness and relevance.

Results: Experience has been reported for a wide variety of alternative therapies in the treatment of chronic idiopathic and physical urticarias. Evidence for most agents is limited to anecdotal reports. The therapies reviewed are also categorized based on criteria of safety, efficacy, convenience, and cost. The less preferred alternative agents in the second part of this review are divided between third-line therapies and others that are unable to be firmly recommended or that seem promising but lack substantial evidence.

Conclusions: Third-line alternative agents should be considered in patients with chronic urticaria who are severely affected and unresponsive to antihistamines and second-line therapies. Although monitoring for toxicity is important in management with third-line agents, safety remains favorable for most agents compared with corticosteroids.

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Off-label disclosure: Drs Morgan and Khan have indicated that most of the medications discussed represent off-label use, as mentioned in the article.

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Instructions for CME credit

1. Read the CME review article in this issue carefully and complete the activity by answering the self-assessment examination questions on the form on page 527
2. To receive CME credit, complete the entire form and submit it to the ACAAI office within 1 year after receipt of this issue of the *Annals*.

INTRODUCTION

The second part of this review continues with alternative therapies for refractory chronic urticaria (CU) that are considered less preferred than previously surveyed second-line drugs, agents unable to be firmly recommended, and newer promising agents that lack substantial evidence. Criteria resulting in classification of these agents include potential for more serious adverse effects, evidence that is more limited or arguing against efficacy, inconvenience, intensive monitoring requirements, and high cost. Nevertheless, these less preferred alternative agents merit review, to foster understanding of the expanded management options available to clinicians. The term *alternative* is preferred for these therapies that may also be appropriately termed *immunosuppressive*, *immunomodulatory*, or *steroid sparing* because not all agents fit these descriptions in all circumstances.

Urticaria of chronicity longer than 6 weeks and with an autoimmune or idiopathic basis (CIU) will remain the focus of this review, alongside relevant experience involving physical urticarias, CU combined with a significant angioedema component, and urticarial vasculitis. Therapies for urticaria in the context of thyroiditis, *Helicobacter pylori*, herpesviruses, progestins, and Schnitzler syndrome exceed the scope of this discussion and are not reviewed.

In general, failure of first-line agents, such as high-dose or combination antihistamines, and adequate therapeutic trials of various second-line agents may prompt investigation into the appropriateness of third-line agents for individual patients with severe refractory CU. Corticosteroids remain the standard comparator for alternative therapies, such that criteria used to judge the merits of each alternative agent must be weighed against the high toxicity and lack of disease-modifying effect, yet high efficacy and low cost, of corticosteroids. Relevant practical variables, such as dosage and titra-

Affiliations: * Division of Allergy and Immunology, University of Texas Southwestern, Dallas, Texas; † Allergy, Asthma, and Immunology of North Texas, McKinney, Texas.

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tion, time to response, possibility of inducing remission, suggested monitoring, and level of evidence,[1] for each agent are given (Table 1). As with second-line agents, frequent follow-up by the clinician is important because of the need for close monitoring for toxicity in patients taking alternative agents for off-label use.

ALTERNATIVE THERAPIES FOR REFRACTORY CU: THIRD-LINE AGENTS

Androgens

Androgens are well established in treating hereditary angioedema but are less frequently used for CU. A major mechanism of action is stimulation of hepatic synthesis of various proteases.[2] Androgens may also exert anti-inflammatory effects by interfering with endogenous sex steroids[3] and suppressing leukocyte activation.[4] The first studies were performed in physical urticarias in which low levels of certain proteases were thought to be important. A randomized controlled trial[5] found danazol effective in 17 male patients with cholinergic urticaria, with a corresponding increase in α_1-antichymotrypsin. Other series[6,7] found similar efficacy. A case of aquagenic urticaria in a patient with human immunodeficiency virus responded dramatically to stanozolol.[8]

Androgens have also been studied in CIU. An early series[9] demonstrated varying degrees of symptom relief in 5 female patients receiving corticosteroids, with which stanozolol was suggested to have been synergistic. Recently, a relatively large (n = 58) 12-week, randomized, double-blind, placebo-controlled study[10] compared stanozolol, 2 mg twice daily, with placebo in patients with CIU refractory to cetirizine. The stanozolol group had a greater clinical response with respect to frequency of marked improvement (65% vs 29%) and mean reduction in clinical scores. Adverse effects were reported as "infrequent," with 2 patients having transient hypertransaminasemia that normalized without treatment cessation. This study is limited by little information on prior treatment and the observation that both groups seemed to have continued reduction in urticarial activity that had not plateaued at the end of the study.

Use of androgens may see particular application for physical urticarias. Androgens are disadvantaged by wide-ranging adverse effects that may affect numerous organ systems. Virilizing and dysmetabolic adverse effects may be distinctly troublesome, for which monitoring is recommended. Although androgens still compare favorably with corticosteroids in many situations, adverse effects, particularly with long-term use, limit their application to third-line status, especially in females.

Methotrexate

Methotrexate possesses anti-inflammatory, antiproliferative, and potentially immunomodulatory activities. Mechanisms relevant to urticaria include reduced neutrophil accumulation in inflamed skin,[11] diminished activated leukocyte adhesiveness and other adenosine-mediated anti-inflammatory properties,[12] decreased leukotriene synthesis,[13] and alteration in cytokine activity.[14] The earliest case report described a single patient with CIU with a long period of drug-free remission after methotrexate administration.[15] Another report[16] detailed 2 patients with CIU in whom second-line agents had failed but who responded to methotrexate within 1 to 2 weeks; however, both patients required maintenance methotrexate therapy for continued benefit. The researchers also mentioned knowledge of methotrexate failures. To our knowledge, the largest series[17] to date described 7 patients with CIU, all of whom seemed to achieve benefit within 1 to 2 weeks of starting methotrexate therapy. There was no comment on whether drug-free remission was seen, but the drug was well tolerated, with "few" adverse effects. The only other report involved a patient described as having urticarial vasculitis but whose biopsy result and clinical picture may also fit severe CIU. This case was notable for remission of at least 7 months after discontinuing a 4-month trial of lower-dose methotrexate (7.5 mg/wk).[18] One negative report[19] described exacerbation of urticarial vasculitis by methotrexate.

Based on a limited number of reports, methotrexate may be highly efficacious and capable of bringing about rapid and prolonged remission in certain patients. Because adverse effects may be serious and frequent monitoring is advised, methotrexate should be reserved for intractable cases in which other alternative agents have failed.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is the alternative agent with theoretically the most immunomodulatory potential in urticaria. Mechanisms of interest have been reviewed elsewhere but may include modulation of cell adhesion, immunoregulatory molecules, complement function, cytokine levels, autoantibodies, and anti-idiotypic networks, although the exact basis remains unclear.[20] Success was first reported in an open trial of 10 patients with CIU who were treated with 5 days of IVIG.[21] All were carefully selected, with positive autologous serum skin test (ASST) and basophil histamine-release test results. Other agents, including corticosteroids and various alternative agents, had failed in many of the patients. All patients were deemed to have had responses ranging from complete and lasting remission to modest transient benefit. The 3 patients who exhibited complete remission (1 after a second course) were symptom free at least 3 years after the last course of IVIG. The lowest dose described was 0.2 g/kg, repeated 1 day every 4 weeks, which produced benefit in a patient with CIU.[22] At a dose of 2 g/kg infused once, a different patient with CIU experienced benefit within 48 hours that lasted 7 months.[23] However, repeating the infusion produced only moderate benefit that failed to persist. In 2 other reports,[24,25] a 5-day infusion resulted in 2 complete responses, 1 partial benefit, and 1 failure among 4 patients with CIU. Failures have been reported elsewhere.[19,26]

The IVIG experience in physical urticarias is similarly limited. Clinical response has been documented in 5 of 8 patients with delayed-pressure urticaria (DPU), using 2 g/kg infused more than 2 to 3 days. Sustained remission was

Table 1. Third-Line Alternative Agents for the Treatment of Chronic Urticaria

Described doses and regimens according to class of agent	Time to response	Time to relapse	Potential for remission	Adverse effects	Suggested monitoring	Level of evidence/ strength of recommendation[1]
Attenuated androgens						
Danazol, 400–600 mg/d orally (divided); or stanozolol, 1–5 mg/d orally (divided)	1 day to 2 weeks	Several days	+	Virilization, vasomotor symptoms, weight gain, and dysmetabolic features (hypertension, hyperlipoproteinemia, and cardiotoxicity); rarely, hepatotoxicity (hepatitis, cholestasis, and neoplasia), polychythemia, photosensitivity, and hemorrhagic cystitis; caution: females, children, thrombotic complications, and porphyria	Baseline: liver enzymes, lipoproteins, blood cell counts, urinalysis, and consider liver or spleen ultrasonography; follow-up: same, every 6 mo	Ib/B
Antifolate antimetabolite						
Methotrexate, 7.5–15 mg/wk orally; consider coadministration of folate	Several days to within 2 weeks	Within 2–3 weeks	+	Gastrointestinal complaints, stomatitis, marrow suppression, rash, hepatotoxicity, alopecia, and infections; caution: ensure dosing is understood to be weekly (not daily) and embryotoxicity	Baseline: blood cell counts, renal function, and liver enzymes; follow-up: blood cell counts monthly and renal function, liver enzymes every 1–2 months or more frequently in settings of increasing blood level or suspected toxicity	IIb/C
Immunoglobulin						
IVIG, 0.2–2.5 g/kg infused over 2–5 days; may require successive monthly courses	Several days to several weeks after starting	Several days to several months	++	Flushing, myalgias, headache, fever, backache, nausea, chest tightness, wheezing, and hemodynamic changes; rarely, aseptic meningitis and anaphylaxis	Baseline: blood cell counts, liver enzymes, renal function, and viral hepatitis studies; consider IgA level in some cases	IIb/C
Phototherapy						
Protocol varies by operator and UV modality	Several days to several weeks	Several days to several months?	++	Photoaging, cutaneous neoplasia, pruritus, dyspigmentation, nausea, headache, and fatigue; caution: photosensitivity disorder, porphyria, and coadministration of methotrexate or hydroxychloroquine	Baseline: skin examination; patients may need to wear UV-A–blocking eye protection; follow-up: same	Ib/C
Anticoagulants						
Warfarin, with target INR of ≥2; or heparin, 5000 U every 12 h	Several days	Several days	±	Hemorrhagic complications and osteoporosis (heparin); rarely, skin necrosis, cholesterol embolization, hepatotoxicity, and heparin-induced thrombocytopenia; caution: embryotoxicity	Baseline: INR for warfarin; consider blood cell counts and risk factors for bleeding complications; follow-up: same	IIb/C
Nitrogen mustard (alkylating agent)						
Cyclophosphamide, intravenously, 500 mg every 2 wk, increasing by 100 mg each successive pulse until 1500 mg/mo; often coadministered with dexamethasone and agents for prophylaxis of cystitis	1 to several months	Unknown	++	Gastrointestinal complaints, malaise, alopecia, marrow suppression, and stomatitis; rarely, rash, cystitis, delayed neoplasia, immune deficiency, and infertility	Baseline: blood cell counts, renal function, urinalysis, and liver enzymes; follow-up: periodic blood cell counts, urinalysis; maintain cumulative dose of <50 g	III/D

Continued

Table 1. Third-Line Alternative Agents for the Treatment of Chronic Urticaria (Continued)

Described doses and regimens according to class of agent	Time to response	Time to relapse	Potential for remission	Adverse effects	Suggested monitoring	Level of evidence/ strength of recommendation[1]
Dihydropyridine calcium channel blocker						
Nifedipine (instant release), 5–20 mg orally every 8 h	Within 1 week	Several days	−	Hypotension and peripheral edema; rarely, flushing, lightheadedness, and gastrointestinal complaints	Baseline: blood pressure; follow-up: same	Ib/C
Gold salts						
Aurothiomalate, 10–100 mg/wk intramuscularly; start at low dose and increase weekly	Several doses (several weeks)	Unknown	+?	Gastrointestinal complaints, photosensitivity, stomatitis, rash, metallic taste, renal dysfunction, and anemia	Baseline: blood cell counts, renal function, and urinalysis; follow-up: blood cell counts and renal function every 1–4 weeks	III/D
Plasmapheresis						
Protocol varies by institution	Several days to several weeks	Several days to several months?	±	Fatigue, gastrointestinal complaints, fever, citrate toxicity (electrolyte disturbances, cramps, and numbness or tingling), and altered coagulation; rarely, humoral immune deficiency, anaphylaxis, and disruption of medication blood levels	Baseline: venous access, blood cell counts, electrolytes, renal function, liver enzymes, and coagulation times; follow-up: hemodynamics, cardiac monitoring, and electrolytes	III/C
Corticosteroid[a]						
Prednisone, up to 1 mg/kg/d (not to exceed 80 mg/d) or equivalent dose of other agent; titrate quickly to lowest effective dose	Several days to 1 week	Variable	−	Mood alteration, adipose and fluid weight gain, hypertension, hyperglycemia, hyperlipoproteinemia, cataracts, raised intraocular pressure, headache, gastrointestinal complaints, dermal atrophy, osteopenia, and infections; caution: children, preexisting psychiatric disorders, and diabetes	Baseline: consider glucose, mental status examination, blood pressure, and lipoproteins; follow-up: same, periodically	IV/D

Abbreviations and symbols: INR, international normalized ratio; IVIG, intravenous immunoglobulin; +, slight possibility; ++, may be expected in some patients; ±, unlikely; −, none; ?, a level of uncertainty regarding the drug in question because of sparse evidence.
[a] Listed for comparison purposes.

demonstrated in 3 patients, although 1 patient required multiple infusions.[27] A patient with solar urticaria had complete response after 3 courses of IVIG and remained disease free at 1-year follow-up.[28] Another patient required concomitant phototherapy for optimal benefit.[29] Favorable response in hypocomplementemic urticarial vasculitis has been reported recently.[30]

Intravenous immunoglobulin is a reasonably safe therapy familiar to many specialists who care for urticaria. Response seems to be rapid, with possibility of true disease-modifying effect in some responders. Adverse effects are generally predictable and manageable. The optimal dose and number of infusions to attempt are unclear. Based also on expense and inconvenience without better assurance of clinical benefit, IVIG should be considered a third-line therapy.

Phototherapy

Phototherapy comprises UV-A therapy with coadministration of psoralen (PUVA) or without coadministration of psoralen and UV-B therapy. Efficacy in phototherapy seems to be maximal for areas of irradiation, suggesting local mediators and cells as primary targets. Phototherapy may also decrease histamine release from mast cells.[31] One open trial[32] in solar urticaria found PUVA more effective than H_1 antihistamines. An earlier case report[33] described long-lasting remission after discontinuation. Another patient with solar urticaria who partially responded to PUVA but could not tolerate adverse effects improved while undergoing extracorporeal photochemotherapy daily for 2 days, then every 2 weeks for 8 months.[34] However, the patient relapsed 8 weeks after discontinuing photopheresis.

Phototherapy has also been studied in other physical urticarias and in CIU. The first such report[35] documented modest transient improvement using PUVA for CIU. Although PUVA is thought to add additional efficacy vs UV-A, a trial[36] with 19 patients with CIU found no difference between PUVA and UV-A, with both groups experiencing modest clinical benefit. A series[37] of 15 patients with physical urticarias (cold, cholinergic, and dermographic) responded better to broadband UV-B than those with CIU. A large retrospective series[38] of 88 patients with CIU showed benefit in 72% of courses of narrowband UV-B, including 27% of 95 courses with complete response. Telephone follow-up several years later revealed 33% remained clear and 45% had lasting benefit. Although phototherapy is often regarded mainly as a treatment for solar urticaria, other physical urticarias and CIU may derive a variable degree of clinical benefit when this modality is available. Some responders seem to enjoy long-lasting improvement.

Anticoagulants

Speculation about the intertwining role of coagulation and fibrinolysis with the inflammatory pathways in urticaria led to investigation of the role of drugs affecting coagulation. Antifibrinolytic and anticoagulant agents may act at various places in the coagulation-fibrinolysis-inflammatory cascades capable of shifting the balance away from prourticarial mediators.[39] Soon after the first report[40] investigating a kallikrein inhibitor in urticaria, a randomized controlled trial[41] using aprotinin revealed an impressive 81% response rate in 52 patients with a mixture of CIU, cold urticaria, acute urticaria, and angioedema. The response rate was higher if patients with acute urticaria were excluded. Best results were observed in atopic patients or in those with an angioedema component. Suggested mechanisms include inhibition of antibody formation and proteolytic enzymes, such as kallikrein (and its precursors) and C1 esterase inhibitor. Experience with tranexamic acid was described in an initial favorable report,[42] but also a small, negative, randomized, controlled trial.[43]

Anticoagulants have also been investigated. Thrombin is involved in selectin and interleukin (IL) 8 induction, leading to neutrophil adhesion and activation, so that thrombin inhibition may exert anti-inflammatory effects.[44] Heparinized autologous serum can reduce the urticarial response in the ASST, possibly by direct disruption of histamine-releasing factors.[45] The generation of thrombin, a protease able to activate mast cells, has also been associated with CIU.[46] Several case reports[47,48] have suggested efficacy of warfarin in CIU, including patients with a strong angioedema component. The only published trial[49] treated 8 patients with CIU with open-label warfarin titrated to an international normalized ratio of 2 to 2.5. Of 6 patients with benefit, 3 underwent a double-blind placebo-controlled trial of warfarin vs placebo for 4 months. Pruritus and angioedema scores significantly improved, but urticarial scores were not measured. The sole contradictory report[50] found that 3 of 4 patients with concomitant angioedema experienced no change or even worsened while taking warfarin. Subcutaneous heparin was reported to work rapidly and completely in a patient in whom warfarin and other alternative therapies had failed.[51] Benefit was highly dependent on continued dosing, with immediate relapse on cessation of home injections.

The potentially life-threatening hemorrhagic risk and need for frequent international normalized ratio monitoring relegate warfarin to third-line status. Similarly, heparin cannot be considered in many patients with intractable CIU. The case of response to heparin in which warfarin had failed suggests cross-efficacy should not be assumed. For the rare patient with CIU who has a simultaneous indication for anticoagulation, it may prove worthwhile to evaluate the efficacy of heparin or warfarin.

Cyclophosphamide

Cyclophosphamide has generally been reserved for patients in whom multiple other alternative agents have failed. Cyclophosphamide is thought to target plasma cells producing the autoantibody responsible for disease manifestations in autoimmune CIU[52]; this might explain the long latency period to and gradual character of clinical improvement noted in available reports. The first published reports described sustained remission in patients with urticarial vasculitis in whom numerous other agents had failed; after reaching the maximum cumulative dose, maintenance therapy with IVIG[53] or mycophenolate[54] was used. Evidence for CIU consists of 2 separate patients in whom multiple other alternative agents had failed. During an 8-month period, improvement began 4 weeks into the initial infusions and evolved into complete resolution by 6 months.[55] The patient continued to be asymptomatic 12 months after the last infusion. Another patient refractory to cyclosporine received cyclophosphamide orally at a higher dose, 1.5 mg/kg 5 days a week, yielding a total monthly dose of 2,000 mg/kg.[56] At 1 month, CIU severity was reduced 50% with nearly complete response at 6-month and 1-year follow-ups. Both patients converted to having ASST negative results. Low oral doses have also been tried in dermographic urticaria.[57] Failures have also been reported, although it is unclear if a sufficient dose or duration was used.[58]

In summary, cyclophosphamide may well be a highly effective and truly immunomodulatory therapy, but because of expense, inconvenience, need for monitoring, risk of serious adverse effects—including delayed secondary neoplasia and hemorrhagic cystitis—and relative paucity of published evidence, this agent should be reserved as a last resort.

Calcium Channel Blockers

Dihydropyridine calcium channel blockers are not generally considered immunomodulatory or immunosuppressive agents, yet by serendipity, nifedipine attracted interest as a potential antiurticarial agent. The mechanism of action is unclear but may involve inhibition of stimulated T-lymphocyte proliferation[59] and mast cell mediator release.[60] Although

early cases suggested efficacy,[61,62] the 2 available randomized controlled trials yielded conflicting results. The first examined 18 patients with symptomatic dermographism and found no response at either 5 or 10 mg thrice daily. The researchers speculated that the dose used may have been too low.[63] A different randomized, controlled, crossover trial demonstrated benefit in 7 patients with CIU taking doses up to 20 mg thrice daily.[64] Notably, patients experienced mild adverse effects attributable to nifedipine.

Interest in calcium channel blockers seems to have waned since these reports. Fairly rapid response after achieving the target dose, relative familiarity with prescribing, and wide availability are advantages. Relatively frequent adverse effects relating mostly to hemodynamics and requirement for blood pressure monitoring are disadvantages, but a trial might be reasonable for patients with CU with concurrent indications for this class of drug.

Chrysotherapy

Gold salts constitute an infrequently used agent for urticaria. Mechanisms include suppression of cellular and humoral immunity and other anti-inflammatory actions, such as inhibition of lysosomal enzymes, suppression of prostaglandin synthesis, and modulation of initial complement component function.[65] Only 1 published case[66] described efficacy for a patient with urticarial vasculitis at the low dose of 10 mg/wk. This patient had previously responded to dapsone but discontinued this therapy because of adverse effects. Although gold may be effective in some patients, perhaps at lower doses than used elsewhere, and has some potential for immunomodulatory action, paucity of evidence, adverse effects, need for monitoring, and expense argue for trying other alternative agents first.

Plasmapheresis

Like phototherapy, plasmapheresis has been mostly associated with treatment of solar urticaria. The mechanism of action is thought to involve removal of autoantibody ("serum factor") and inflammatory mediators.[67] As a predictive factor, most authorities recommend plasmapheresis for serum factor–positive solar urticaria; a small comparison demonstrated modest benefit in 2 serum factor–positive patients but none in 1 serum factor–negative patient.[68] Various case reports[69,70] have demonstrated clinical benefit as soon as the first day in some patients, but the possibility of long-term remission has been observed less consistently. Phototherapy has also been combined with plasmapheresis to convert partial response into full remission.[71] Only 1 series[72] has examined plasmapheresis for CIU, in which 3 of 8 patients derived modest benefit. However, most eventually relapsed, because of hypothesized reaccumulation of autoantibody. Plasmapheresis may be appropriate for refractory solar urticaria with positive serum factor and when pharmacotherapy and phototherapy have failed. For CIU, modest efficacy, expense, inconvenience, and limited experience restrict the use of plasmapheresis to exceptional circumstances.

ALTERNATIVE AGENTS NOT CURRENTLY RECOMMENDED

A variety of other alternative therapies cannot be recommended because of lack of published positive experience. Azathioprine has been used in many parallel indications with other alternative agents; however, no direct published reports or trials are available for CU. Indirect references in other reports, mostly for urticarial vasculitis, have been uniformly disappointing.[19,26,53]

Several asthma medications have also been used for urticaria, with mixed results. Cromolyn has been attempted for nonsteroidal anti-inflammatory drug (NSAID)– and food additive–induced urticaria unsuccessfully.[73,74] One positive report[75] of benefit with inhaled cromolyn in 3 patients with CIU who did not have asthma has not been duplicated. β-Agonists may suppress the wheal-and-flare response[76] and have also been used for CIU and physical urticarias. Terbutaline, up to 25 mg thrice daily, was found effective where antihistamines had failed; among 24 patients, those with CIU had more benefit than those with physical urticarias.[77] The only other favorable reports[78,79] described patients with cold and other urticarias refractory to antihistamines who had benefit while taking a combination of ketotifen and terbutaline. However, other open series[76,80] found no benefit. A randomized, double-blind, multiarm, crossover study[81] found terbutaline inferior to antihistamines in 19 patients with CIU. From data to date, neither cromones nor β-agonists represent effective therapies in the treatment of CIU.

Available published data on methylxanthines suggest the possibility of benefit but with wide variability in degree of response. In the earliest report,[82] only 3 of 15 patients (20%) with CIU experienced complete response after a 4-week course of theophylline, whereas 6 (40%) had no significant response. A recent, double-blind, placebo-controlled study[83] of 134 patients with CIU receiving maintenance cetirizine showed moderate benefit in the group treated with add-on theophylline compared with placebo. The 54 patients who completed the theophylline group exhibited reduction in overall visual analog scores but not pruritus. Several weeks seemed necessary for benefit to become apparent.

Experience in physical urticarias is similarly mixed. Benefit for DPU was demonstrated in an open crossover trial of 23 patients. Response became apparent around the second month for the theophylline plus cetirizine group; benefit required continuation of medication in responders. A combination of aminophylline plus terbutaline showed a wide spectrum of response in 42 patients with cold urticaria; 5 had complete response by 1 week, and 2 had no apparent benefit, with the remainder having modest benefit after more than 2 to 6 months of open follow-up therapy.[84] Adverse effects were significant, with 3 having cardiac events that mandated cessation of therapy and 19 others having less severe problems. Although these studies suggest a long period of therapy may yield benefit, this seems to be in a few patients and modest overall. These data seem to support prevailing opinion that

theophylline might be at best modestly effective but has significant liability for adverse effects and requires monitoring of drug levels.

Indomethacin is the main NSAID studied for use in physical urticarias and urticarial vasculitis. Benefit has been most consistent in patients with pain and constitutional symptoms.[85,86] These benefits may primarily be because of an analgesic rather than antiurticarial effect. Studies[87,88] suggesting efficacy of rofecoxib in CIU have not been replicated with available selective cyclooxygenase inhibitors. Combined with the well-known propensity for NSAIDs to trigger urticaria in certain patients, they are unable to be recommended for general use in CU without further study.

Interferon alfa has shown disappointing results in 2 published series of patients with CU. A regimen of 3×10^6 U thrice weekly for 8 weeks failed to benefit patients with a mixture of CIU, DPU, and cold urticaria.[89] In another open trial,[90] 4 of 8 patients with CIU achieved partial response; however, efficacy seemed to diminish over time. The sole successful report[26] described a patient with urticarial vasculitis in whom numerous alternative agents had failed but who achieved benefit with interferon alfa-2a. Considering the expense and potential for troublesome adverse effects without better evidence for efficacy, use of interferon alfa for CU must be advised against.

Autohemotherapy involves parenteral injection of autologous blood in an attempt to desensitize patients to endogenous prourticarial factors thought to be implicated in CIU. After an initial promising report,[91] the first formal investigation for CIU has recently been published. In this single-blind placebo-controlled trial, 56 patients with CIU were randomized to either autologous, whole, untreated blood, 5 mL intramuscularly (2.5 mL the first week), or isotonic sodium chloride solution for 8 weeks.[92] Patients with ASST positivity experienced moderate reduction in urticarial lesions, decreased antihistamine use, and improved quality of life. The ASST-negative patients did not have appreciable benefit. It is advisable that additional favorable evidence should be accumulated at more centers before autohemotherapy can be widely considered in the treatment of refractory CIU.

There remains no evidence that allergens play a role in CU other than in unusual circumstances. Immunotherapy to sweat extract has been reported to be successful in the treatment of cholinergic urticaria, presumably because of induction of tolerance to endogenous allergens.[93] A single report[94] describes a case of CU due to grass pollinosis, treated successfully with desensitization. Seasonal CU occurring during the grass season, with severity beyond ordinary contact urticaria to grass, resolved after the patient achieved the maintenance dose of Timothy grass. This curiosity aside, routine aeroallergen testing and immunotherapy continues not to be indicated in the management of CIU.

OTHER PROMISING AGENTS WITHOUT SUFFICIENT EXPERIENCE

Several biological agents that seem promising but are too new to have sufficient experience to warrant inclusion among second-line agents are briefly discussed herein. The first published use of omalizumab**,** a monoclonal antibody directed against IgE, has been reported for cold urticaria.[95] An 11-year-old girl with cold urticaria and extrinsic asthma, both refractory to conventional therapy, experienced partial response between 2 and 4 weeks after the initial dose. Progression to complete response occurred after 5 months. Relapse occurred on missing 1 month of injections, with prompt restoration of benefit after resuming therapy. Expense and inconvenience remain barriers to broader application, but of the agents lacking more evidence, omalizumab seems most promising based on speculation that patients with CIU with circulating IgE or IgE receptor autoantibodies might experience similar benefit.

Inhibitors of tumor necrosis factor α (TNF-α) and IL-1 have recently shown promise. After 5 days of etanercept, 25 mg twice weekly, for refractory psoriasis, DPU symptoms resolved completely in a patient whose symptoms were only partially controlled with cetirizine.[96] After 5 months, this patient was switched to infliximab for better control of psoriasis and remained free of DPU symptoms while receiving this agent at 1-year follow-up. Similarly rapid impressive benefit was noted in 1 patient with urticarial vasculitis after starting anakinra, an antagonist of IL-1.[97] No adverse effects were noted with either treatment. Because TNF-α has been shown to be up-regulated in lesional and nonlesional skin in various types of CU,[98] inhibitors of TNF-α and IL-1 may indeed be effective agents, but further experience is required.

Rituximab is another biological therapy of potential interest for autoantibody-mediated disorders. B lymphocytes are targeted, similar to cyclophosphamide, but with the potential for fewer adverse effects. One report[99] detailed a patient with hypocomplementemic urticarial vasculitis in whom cyclophosphamide, prednisone, and other alternative agents had failed. A 4-week course of rituximab, 375 mg/m^2, caused "rapid" improvement, with tapering of corticosteroids and drug-free remission from the urticaria/angioedema of unspecified duration. No adverse effects were observed. However, the same regimen administered to a patient with CIU in whom numerous alternative therapies had failed resulted in no improvement.[100] Rituximab seems to be an interesting alternative agent, but results of published experience are mixed and limited.

CONCLUSION

Third-line therapies retain value and interest in the management of CU refractory to antihistamines and second-line agents. In most situations, third-line agents can be appropriate and preferable to systemic corticosteroids. The practitioner with sufficient skill and knowledge may successfully apply third-line agents and others we have not classified as recom-

mended safely and appropriately for selected patients with CU.

Clearly, interest in broadening the pharmacologic armamentarium is not a recent phenomenon. A review[101] from half a century ago describes a bewildering variety of alternative treatments for CU. The level of evidence for many of these formulations would not meet the least rigorous of today's standards, but evidence for several agents that continue to appear in our list has improved only marginally in the past 50 years. Future management of CU will be challenged to improve therapy for disease refractory to standard medications through further elucidation of the underlying pathophysiological features and clinical trials to bolster evidence for many promising but understudied therapies.

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Requests for reprints should be addressed to:
David A Khan, MD
Division of Allergy and Immunology
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX 75390-8859
E-mail: dave.khan@utsouthwestern.edu

Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

Credits: The American College of Allergy, Asthma and Immunology is accredited by the Accreditation Council for Continuing Medical Education to sponsor medical education for physicians. ACAAI designates each Annals CME Review Article for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credits commensurate with the extent of their participation in the activity.

CME Examination

1–5, Morgan M, Khan DA. 2008;100:517–526.

CME Test Questions

1. Which of the following medications has demonstrated efficacy for chronic urticaria in a randomized controlled trial?
   a. cyclophosphamide
   b. intravenous immunoglobulin (IVIG)
   c. methotrexate
   d. stanozolol
2. B-lymphocyte suppression is a major mechanism of action for which of the following medications?
   a. infliximab
   b. omalizumab
   c. natilizumab
   d. rituximab
3. Which of the following therapies has the lowest level of evidence for efficacy in chronic urticaria?
   a. azathioprine
   b. nifedipine
   c. phototherapy
   d. warfarin
4. Which of the following therapies would likely be most efficacious in a patient with solar urticaria?
   a. cyclophosphamide
   b. danazol
   c. methotrexate
   d. phototherapy
5. Delayed secondary neoplasia is a potential adverse effect seen most commonly with which of the following therapies?
   a. cyclophosphamide
   b. etanercept
   c. IVIG
   d. stanozolol

Answers found on page 544.